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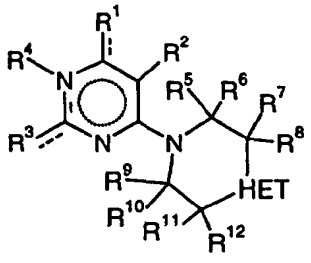
(54) Title: TETRAHYDRO-HETEROCYCLOAZEPINYL PYRIMIDINE DERIVATIVES

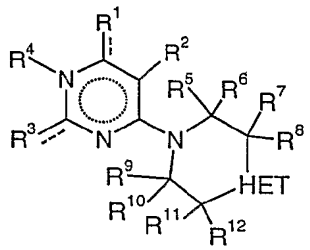


(I)

(57) Abstract: The invention relates to compounds of the general formula (I) wherein HET and R^1 to R^{12} have the significances as defined in the specification, as well as their phamaceutically acceptable salts. The invention further relates to medicaments containing such compounds and a process for the preparation of such compounds. The compounds of formula (I) are group (I) mGluR antagonists and are therefore useful for the control or prevention of acute and/or chronic neurological disorders.

Tetrahydro-heterocycloazepinyl pyrimidine derivatives

The present invention is concerned with nitro- and cyano-1,2,4,5-tetrahydro-heterocycloazepinyl pyrimidine derivatives of the general formula



I

wherein

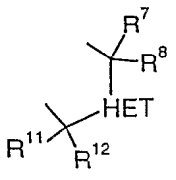
R^1 signifies oxygen, hydroxy, lower alkoxy or 2,2,2-trifluoroethoxy;

R^2 signifies nitro or cyano;

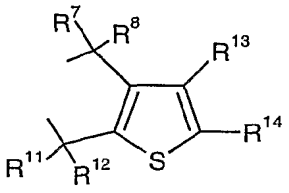
R^3 signifies hydrogen, lower alkyl, oxygen, lower alkoxy, amino, lower alkyl-amino or hydroxy-lower alkyl-amino;

R^4 signifies hydrogen, lower alkyl, lower alkenyl, or is absent, if the adjacent nitrogen atom already is the origin of three bonds as –N= or =N-;

R^5, R^6, R^9 and R^{10} signify, independently from each other, hydrogen or lower alkyl;

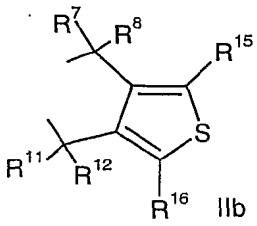


signifies



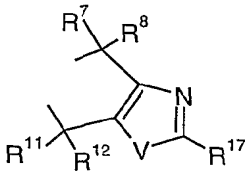
IIa

or



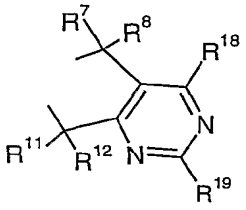
IIb

or



IIc

or



IId

R^7, R^8, R^{11} or R^{12}	signify, independently from each other, hydrogen, lower alkyl, or hydroxy;
R^{13} and R^{14}	signify, independently from each other, hydrogen or lower alkyl;
R^{15} and R^{16}	signify, independently from each other, hydrogen or lower alkyl;
R^{17}	signifies hydrogen, lower alkyl, lower alkoxy, hydroxy or amino;
R^{18}	signifies hydrogen or hydroxy;
R^{19}	signifies hydrogen, lower alkyl, lower alkoxy, hydroxy or amino;
V	signifies NH, S or O; and

the dotted line may be a bond,

as well as with their pharmaceutically acceptable salts in their racemic and optically active form.

It has surprisingly been found that the compounds of general formula I are antagonists at metabotropic glutamate receptors.

In the central nervous system (CNS) the transmission of stimuli takes place by the interaction of a neurotransmitter sent out by a neuron, with another neuroreceptor.

L-glutamic acid, the most commonly occurring neurotransmitter in the CNS, plays a critical role in a large number of physiological processes. The glutamate-dependent stimulus receptors are divided into two main groups. The first main group forms ligand-controlled ion channels. The metabotropic glutamate receptors (mGluR) belong to the second main group and, furthermore, belong to the family of G-protein-coupled receptors.

At present, eight different members of these mGluRs are known and some of these even have sub-types. On the basis of structural parameters, the different second messenger signaling pathways and their different affinity to low-molecular weight chemical compounds, these eight receptors can be sub-divided into three sub-groups:

mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

Ligands of metabotropic glutamate receptors belonging to the first group can be used for the treatment or prevention of acute and/or chronic neurological disorders such as epilepsy, stroke, chronic and acute pain, psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits.

Other treatable indications in this connection are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, opiate addiction, psychoses, anxiety, vomiting, dyskinesia and depression.

Objects of the present invention are compounds of formula I and their pharmaceutically acceptable salts per se and as pharmaceutically active substances, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of the compounds in accordance with the invention in the control or prevention of illnesses of the aforementioned kind, and, respectively, for the production of corresponding medicaments. Furthermore, the use of radiolabeled mGluR1

receptor antagonists of formula I in a binding assay is also an object of the present invention.

Preferred compounds of formula I in the scope of the present invention are those, in which R^2 is NO_2.

Further preferred are compounds of formula I in the scope of the present invention, wherein

R^1 is =O or lower alkoxy and

HET represents a thiophene group.

The following are examples of such compounds:

[rac]-6-(4-Hydroxy-4,5,7,8-tetrahydro-thieno[2,3-d]azepin-6-yl)-2-methyl-5-nitro-3H-pyrimidin-4-one,

2-Methyl-5-nitro-6-(4,5,7,8-tetrahydro-thieno[2,3-d]azepin-6-yl)-3H-pyrimidin-4-one,

6-(6-Ethoxy-2-methyl-5-nitro-pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-thieno[2,3-d]azepine, or

3-Ethyl-2-methyl-5-nitro-6-(4,5,7,8-tetrahydro-thieno[2,3-d]azepin-6-yl)-3H-pyrimidin-4-one.

Also preferred are compounds of formula I in the scope of the present invention, wherein

R^1 is =O or lower alkoxy, and

HET represents a thiazole group.

The following are examples of such compounds:

2-Methyl-6-(2-methyl-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-5-nitro-3H-pyrimidin-4-one,

6-(6-Ethoxy-2-methyl-5-nitro-pyrimidin-4-yl)-2-methyl-5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepine,

3-Ethyl-2-methyl-6-(2-methyl-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-5-nitro-3H-pyrimidin-4-one,

6-(2-Amino-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-2-methyl-5-nitro-3H-pyrimidin-4-one,

6-(2-Amino-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-3-ethyl-2-methyl-5-nitro-3H-pyrimidin-4-one, or

2-Methyl-5-nitro-6-(4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-3H-pyrimidin-4-one.

Further preferred compounds of formula I in the scope of the present invention are those, in which

R^1 is hydroxy and

HET represents a pyrimidine group.

The following are examples of such compounds:

7-(6-Hydroxy-2-methyl-5-nitro-pyrimidin-4-yl)-2-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepin-4-ol, or

2-Methyl-5-nitro-6-(5,6,8,9-tetrahydro-pyrimido[4,5-d]azepin-7-yl)-pyrimidin-4-ol.

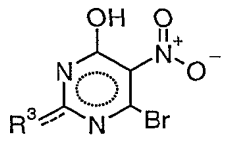
The term "lower alkyl" used in the present description denotes straight-chain or branched saturated hydrocarbon residues with 1-7 carbon atoms, preferably with 1-4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl and the like.

The term "lower alkenyl" used in the present description denotes straight-chain or branched unsaturated hydrocarbon residues with 2-7 carbon atoms, preferably with 2-4 carbon atoms.

The term "lower alkoxy" denotes a lower alkyl residue in the sense of the foregoing definition bonded via an oxygen atom.

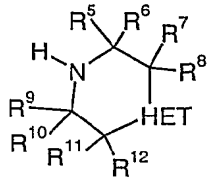
The compounds of general formula I and their pharmaceutically acceptable salts can be manufactured by

a) reacting a compound of the formula



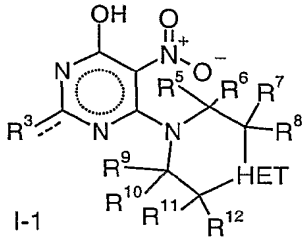
III

with a compound of formula



IV

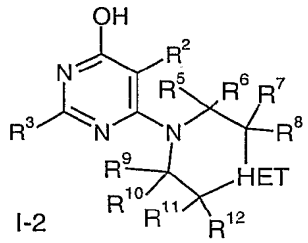
to a compound of formula



I-1

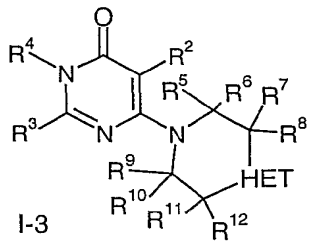
wherein R^3 and R^5 to R^{12} have the significance given above.

b) reacting a compound of formula



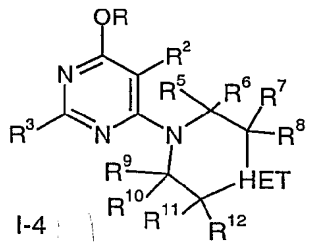
I-2

to a compound of formula



I-3

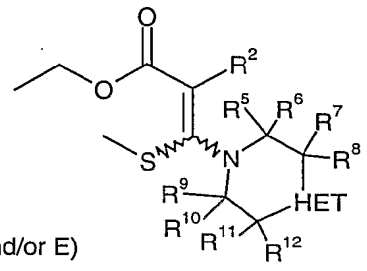
or to a compound of formula



I-4

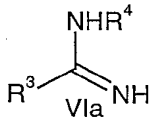
wherein R^2, R^3 and R^5 to R^{12} have the significance given above and R signifies hydrogen or lower alkyl, or

c) reacting a compound of formula



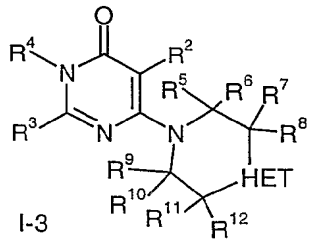
V (Z and/or E)

with a compound of formula



VIa

to a compound of formula



I-3

wherein the substituents have the significance given above,

and, if desired,

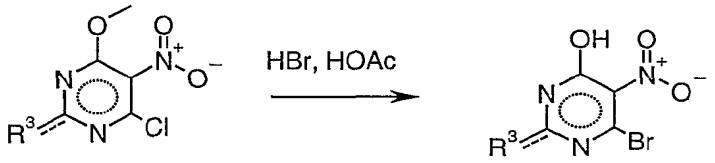
converting a functional group in a compound of formula I into another functional group and, if desired,

converting a compound of formula I into a pharmaceutically acceptable salt.

In the following schemes I to VII and in Examples 1 - 10 the reaction steps and reaction variants a) - c) are described in more detail.

Chloro-methoxy-nitro pyrimidines VII (Scheme I) are known [e.g. 6-chloro-4-methoxy-2-methyl-5-nitro-pyrimidine: Helv. (1958), 41, 1806]. Treatment of the 2-alkyl 6-chloro-4-methoxy-5-nitro-pyrimidines VII with hydrobromic acid in acetic acid preferentially at temperatures between 0 °C and 60 °C gives the 2-alkyl-6-bromo-5-nitro-3H-pyrimidin-4-ones III (Scheme I).

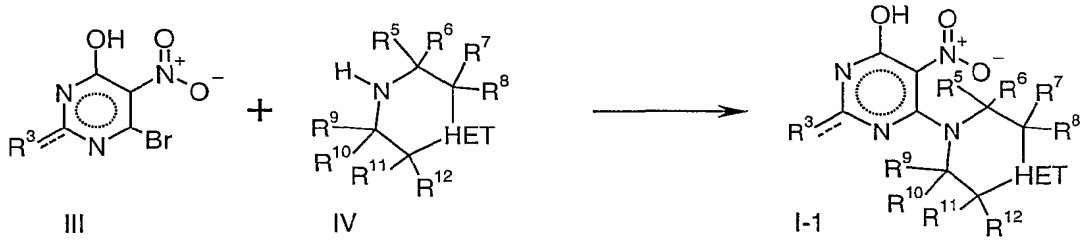
Scheme I



VII III

The 2-alkyl-6-bromo-5-nitro-3H-pyrimidin-4-ones III react with optionally substituted secondary amines IV in the presence of a base like triethylamine in solvents like N,N-dimethylformamide, dimethylsulfoxide, acetone, methyl-ethylketone or tetrahydrofuran at temperatures between 0 °C and 100 °C to the tertiary amines I-1 (Scheme II).

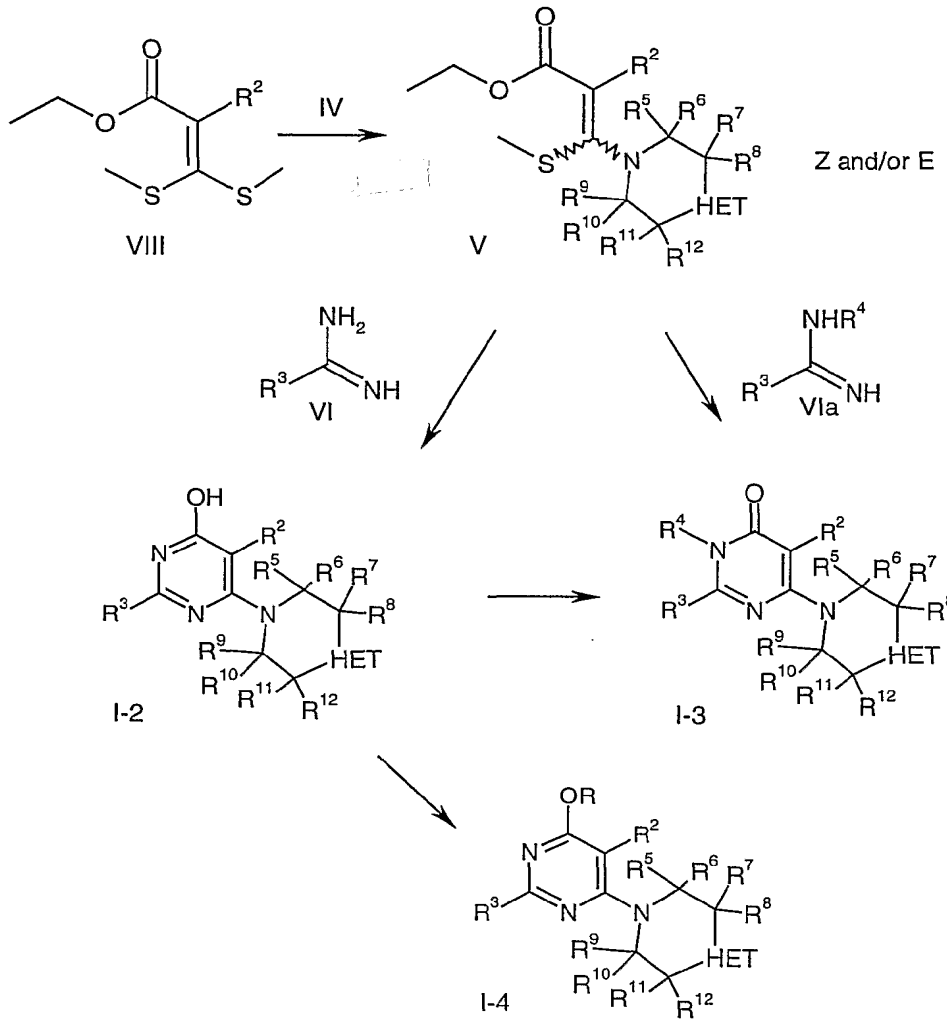
Scheme II



III IV I-1

Bis(methylthio)-acrylates VIII react with optionally substituted secondary amines IV in the presence of bases like potassium carbonate and/or triethylamine in solvents like ethanol, methanol, acetone or methyl-ethylketone at temperatures between room temperature and 100 °C to adducts V, which can be formed as Z-isomer, as mixture of E and Z isomers or as E isomer (Scheme III). Adducts V can be reacted with amidines, urea or thiourea derivatives VI either in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene in N,N-dimethylformamide or dimethylsulfoxide at temperatures between 70 °C and 140 °C or in the presence of sodium ethylate in ethanol preferentially at reflux thus yielding pyrimidineoles I-2 or pyrimidinones I-3.

Scheme III

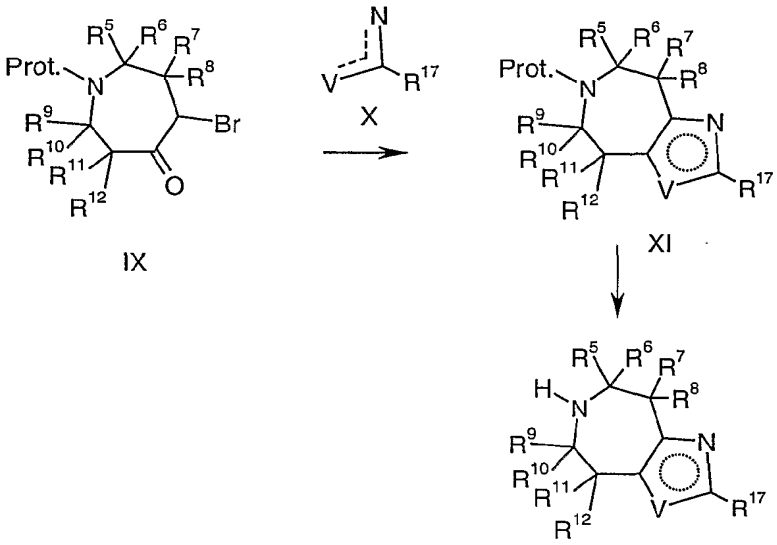


Alkylation of adducts I-2 with R^2 being a cyano or a nitro group (Scheme III) using optionally substituted alkyl halides, tosylates, mesylates or trifluoro-methanesulfonates in solvents like ethanol, methanol, dichloromethane, chloroform, N,N-dimethylformamide, dimethylsulfoxide, acetone, methyl-ethylketone or tetrahydrofuran in the presence of a base like alkali carbonates, e.g. sodium, potassium or cesium carbonate, tertiary amines like triethylamine or ethyl-diisopropylamine, alkali methyl hydrides, like sodium or potassium hydride, or phase transfer catalysts like benzyl-trimethylammonium chloride in the presence of solid or concentrated aqueous sodium hydroxide gives variable mixtures of N- and/ or O-alkylated products I-3 and I-4.

Azepines IV-1 condensed to a heteroaromatic 5-membered ring bearing two heteroatoms can be prepared from bromoazepinones IX (Scheme IV) as e.g. 4-bromo-5-

oxo-azepane-1-carboxylic acid tert.-butyl ester (prepared from 5-bromo-azepan-4-one hydrobromide (1:1) [Ger. Offen. (1989), DE 3820775] with di-tert.-butyldicarbonate in dioxane/aq. sodium hydrogen carbonate solution at room temperature) by reaction with an amide, a thioamide, an urea or a thiourea compound in a solvent like ethanol, dioxane or acetonitrile in the presence of a base like sodium ethylate or triethylamine at temperatures between room temperature and 120 °C followed by removal of the tert.-butoxy carbonyl function with acid, e.g. with hydrogen chloride (aqueous, 37%) in methanol at temperatures between room temperature and 80 °C.

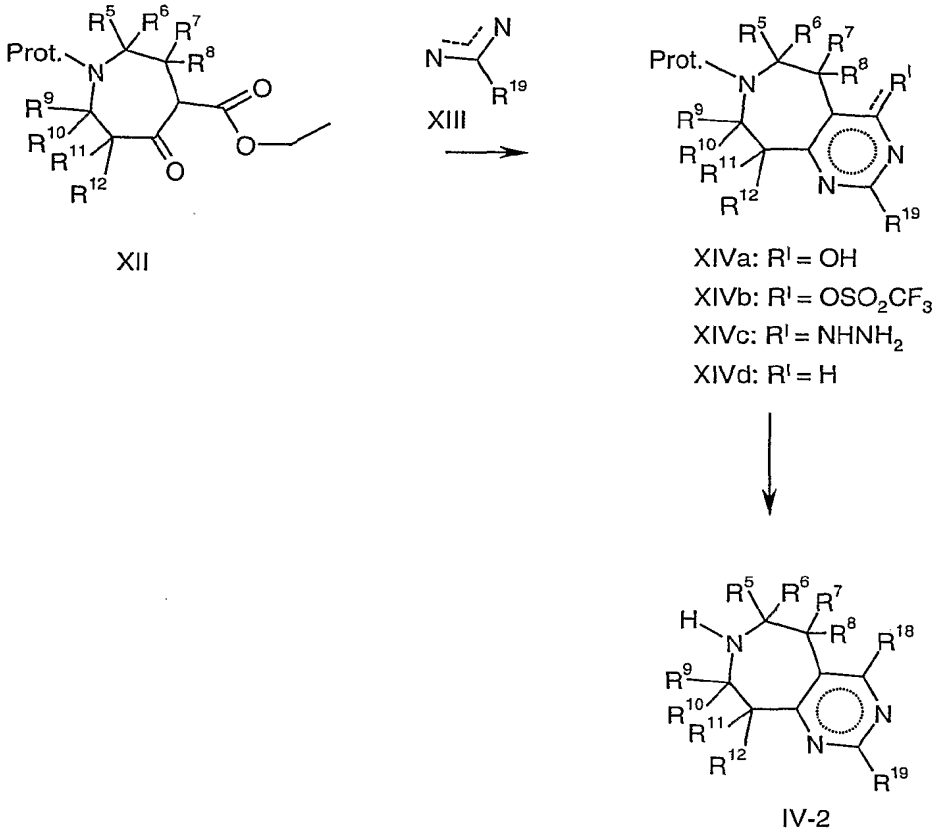
Scheme IV



Azepines IV-2 condensed to a heteroaromatic 6-membered ring bearing two heteroatoms can be prepared from alkoxycarbonyl-azepinones XII as e.g. 4-ethoxy-carbonyl-5-oxo-azepane-1-carboxylic acid tert.-butyl ester [Synthetic Communications 22 (1992), 1249-1258] (Scheme V) by condensation with an amidine XIII in a solvent like ethanol, dioxane or N,N-dimethylformamide in the presence of a base like sodium ethoxide or potassium tert.-butylate at temperatures between 40 °C and 110 °C. The primarily formed compounds XIVa can be further modified by transformation of the hydroxy function into a leaving group, e.g. a trifluorosulfonyloxy function with trifluorosulfonic acid anhydride and a base like triethylamine in an inert solvent like dichloromethane at temperatures between -40 °C and 60 °C, thus giving compounds XIVb. The trifluorosulfonyloxy function in compounds XIVb can then be replaced by a hydrazine moiety by reacting it with hydrazine in a solvent like ethanol preferentially at reflux giving

compounds XIVc. Hydrazino-compounds XIVc can be transformed by silver oxide in ethanol at reflux into the compounds XIVd, a sequence as described in [Bull. Chem. Soc. Jap. (1971), 44(1), 153-8]. Removal of the tert.-butoxy carbonyl function in compounds XIVa or XIVd with acid, e.g. with hydrogen chloride (aqueous, 37%) in methanol at temperatures between room temperature and 80 °C gives then the azepines IV-2.

Scheme V

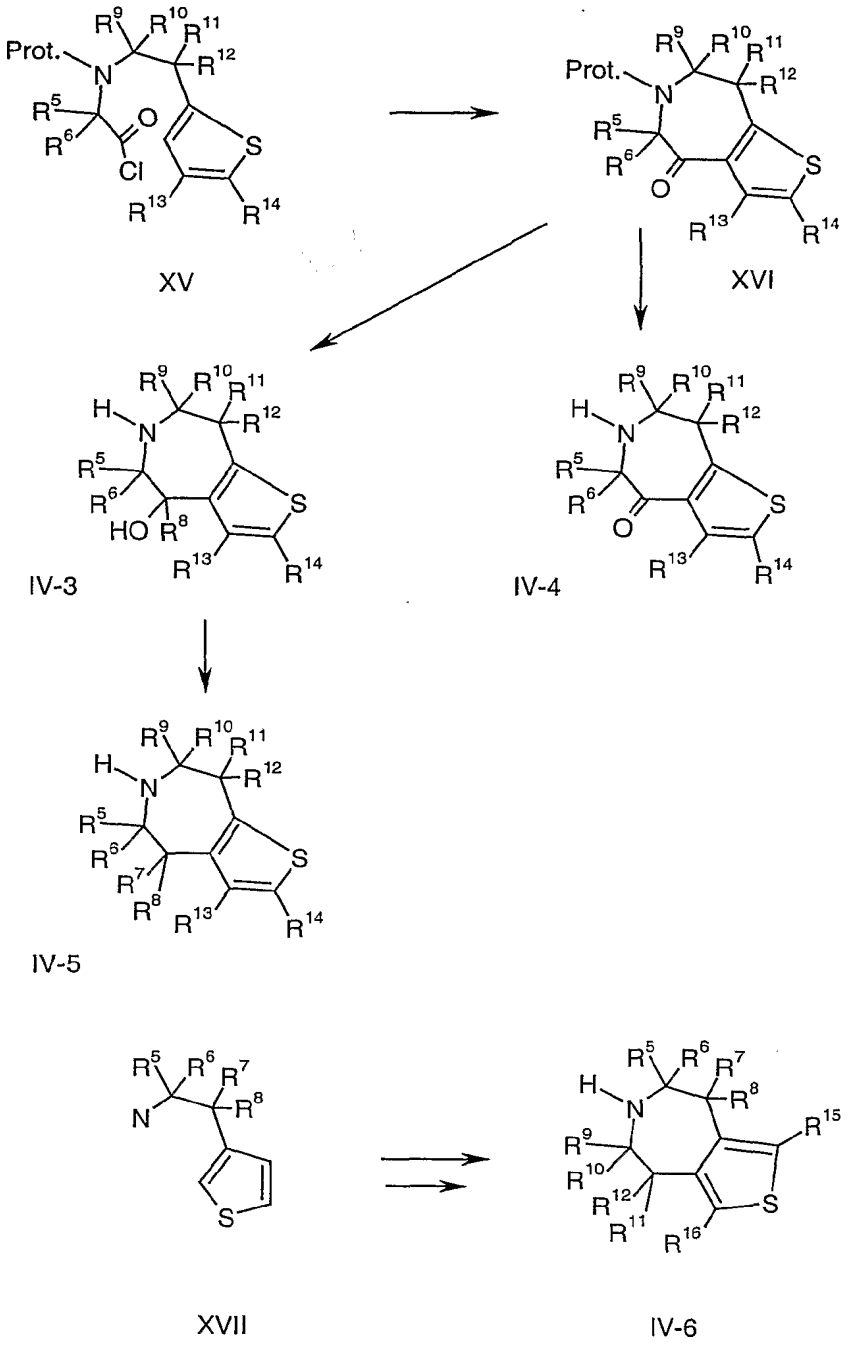


5,6,7,8-Tetrahydro-4H-thieno[2,3-d]azepines IV-3 and IV-5 with or without a hydroxy function at the carbon attached to the thieno moiety are known [J. Heterocyclic Chem. 22, 1011 (1985)]. Precursor acid chlorides XV bearing preferentially a tosyloxy protective function at the azepine secondary nitrogen function are cyclized in an inert solvent like 1,2-dichloroethane, dichloromethane or nitrobenzene in the presence of a Lewis acid catalyst like aluminium trichloride, tin tetrachloride or phosphorous pentachloride at temperatures between -40 °C and 80 °C to yield the protected ketones XVI. Keto thieno[2,3-d]azepines IV-4 are then prepared by cleavage of N-tosyl function with hydrobromic acid in the presence of a scavenger reagent like phenol in a solvent like ethyl acetate at room temperature, whereas hydroxy thieno[2,3-d]azepines IV-3 can be

obtained by simultaneous reduction of the keton function and removal of the N-tosyl protective function by treatment with sodium bis(methoxyethoxy)aluminium-hydride in toluene at reflux. The hydroxy thieno[2,3-d]azepines IV-3 can be further reduced to 5,6,7,8-tetrahydro-4H-thieno[2,3-d]azepines IV-5 with stannous chloride in acetic acid in the presence of hydrochloric acid at temperatures between room temperature and 100 °C.

5,6,7,8-Tetrahydro-4H-thieno[3,4-d]azepines IV-6 isomeric to 5,6,7,8-tetrahydro-4H-thieno[2,3-d]azepines IV-5 can be prepared from 2-thiophen-3-yl-ethylamine derivatives XVII [Eur. Pat. Appl. (1988), EP 274324 A1] in an analogous sequence as described for the thieno[2,3-d]azepines outlined in detail in Scheme VI.

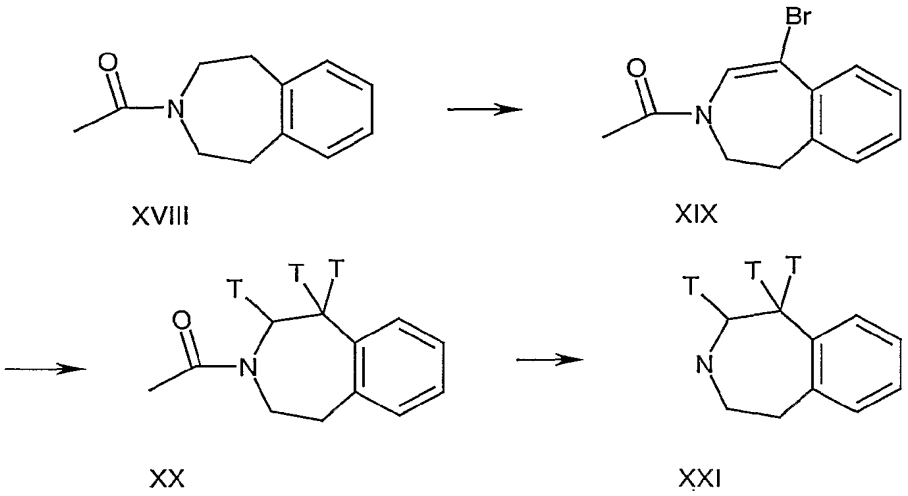
Scheme VI



A labeled compound, for example 1-ethyl-2-methyl-6-oxo-4-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile, is needed for the binding assay for the characterization of mGluR 1 antagonistic properties and can be prepared according to synthesis schemes I – III starting from a labeled amine as the 1,1,2-tritritio-2,3,4,5-tetrahydro-1H-benzo[d]azepine XXI which can be prepared as outlined in

Scheme VII. The 1-(5-bromo-1,2-dihydro-benzo[d]azepin-3-yl)-ethanone XIX can be obtained by reaction of the 1-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-ethanone XVIII [J. Heterocycl. Chem. (1971), 8(5), 779-83] with N-bromosuccinimide in carbon tetrachloride in the presence of a radical initiator like dibenzoylperoxide or 1,1'-azobis-(cyclohexanecarbonitrile) preferentially at reflux. Hydrogenation of the 1-(5-bromo-1,2-dihydro-benzo[d]azepin-3-yl)-ethanone XIX with tritium gas using a palladium or platinum catalyst in solvents methanol, ethanol or an ether like tetrahydrofuran preferentially in the presence of a base like triethylamine gives the 1-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-ethanone XX which can be converted into the 1-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-ethanone XXI with conc. aq. hydrochloric acid in methanol.

Scheme VII



XVIII XIX XX XXI

The pharmaceutically acceptable salts can be manufactured readily according to methods known per se and taking into consideration the nature of the compound to be converted into a salt. Inorganic or organic acids such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like are suitable for the formation of pharmaceutically acceptable salts of basic compounds of formula I. Compounds which contain the alkali metals or alkaline earth metals, for example sodium, potassium, calcium, magnesium or the like, basic amines or basic amino acids are suitable for the formation of pharmaceutically acceptable salts of acidic compounds of formula I.

The compounds of formula I and their pharmaceutically acceptable salts are, as already mentioned above, metabotropic glutamate receptor antagonists and can be used for the treatment or prevention of acute and/or chronic neurological disorders, such as epilepsy, stroke, chronic and acute pain, psychosis, schizophrenia, Alzheimer's disease, cognitive disorders, memory deficits and psychosis. Other treatable indications are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are Huntington's chorea, ALS, dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression.

The compounds of the present invention are group I mGluR antagonists and were tested using the following method:

Binding assay for the characterization of mGluR 1 antagonistic properties

Binding assay with tritiated 1-ethyl-2-methyl-6-oxo-4-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile: HEK 293 cells were transiently transfected with the rat mGluR1a receptor. The cells were collected and washed 3 times with PBS. The cell pellets were frozen at –80 °C. Membranes were prepared from HEK 293 cells transfected with the rat mGluR1a receptor and used in the binding experiments at 10 μg proteins per assay after resuspension in a HEPES NaOH 20mM, pH=7.4 binding buffer. 1-Ethyl-2-methyl-6-oxo-4-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile (S.A 33.4Ci/mmol) was used at 3 nM final concentration. The incubation with variable concentrations of potential inhibitors was performed for 1 hour at room temperature, the incubate was then filtered onto GF/B glass fiber filter preincubated 1 hour in PEI 0,1% and washed 3 times with 1ml of cold binding buffer. The radioactivity retained on the unifilter 96 was counted using a Topcount β counter. After correction for non specific binding the data were normalized and the IC_{50} value calculated using a 4 parameters logistic equation which was fitted to the inhibition curve.

Preferred compounds have an IC_{50} range of 0,001 – 50,00 μM (B-IC_{50}).

In the table below are shown some specific activity data of preferred compounds:

	Example No.	B-IC_{50} (μM)
2-methyl-6-(2-methyl-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-5-nitro-3H-pyrimidin-4-one	1	30
6-(6-ethoxy-2-methyl-5-nitro-pyrimidin-4-yl)-2-methyl-5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepine	2	4.2
3-ethyl-2-methyl-6-(2-methyl-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-5-nitro-3H-pyrimidin-4-one	2	2.1
6-(2-amino-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-2-methyl-5-nitro-3H-pyrimidin-4-one	3	49
6-(2-amino-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-3-ethyl-2-methyl-5-nitro-3H-pyrimidin-4-one	4	6
2-methyl-5-nitro-6-(4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-3H-pyrimidin-4-one	6	43
2-methyl-5-nitro-6-(4,5,7,8-tetrahydro-thieno[2,3-d]azepin-6-yl)-3H-pyrimidin-4-one	9	1.9
6-(6-ethoxy-2-methyl-5-nitro-pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-thieno[2,3-d]azepine	10	0.44
3-ethyl-2-methyl-5-nitro-6-(4,5,7,8-tetrahydro-thieno[2,3-d]azepin-6-yl)-3H-pyrimidin-4-one	10	0.069

The compounds of formula I and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for

example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

In addition, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more compounds of formula I or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/ kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

Finally, as mentioned earlier, the use of compounds of formula I and of pharmaceutically acceptable salts thereof for the production of medicaments, especially for the control or prevention of acute and/or chronic neurological disorders of the aforementioned kind, is also an object of the invention.

Example 1

2-Methyl-6-(2-methyl-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-5-nitro-3H-pyrimidin-4-one

a) 6-Bromo-2-methyl-5-nitro-3H-pyrimidin-4-one

56.6 ml (503 mmol) of hydrobromic acid solution (48% in water) were added dropwise to a solution of 20.5 g (101 mmol) of the 2-methyl-4-methoxy-5-nitro-6-chloro-pyrimidine [Helv. (1958), 41, 1806] in 450 ml of acetic acid and the reaction mixture was stirred at room temperature for 44 hours. It was then evaporated under reduced pressure and the residue formed poured into 500 ml of an ice/water mixture and extracted 3 times with 500 ml of dichloromethane. The combined dichloromethane phases were washed with 100 ml of water and evaporated under reduced pressure. There were thus obtained 16.3 g (69.6 mmol, yield 69%) of the 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one as light yellow solid, which was used without further purification.

b) 2-Methyl-5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepine

The title compound was prepared by the following reaction sequence: i) treatment of the 5-bromo-azepan-4-one hydrobromide (1:1) [Ger. Offen. (1989), DE 3820775] with di-t-butyldicarbonate in dioxane/aq. sodium hydrogen carbonate solution to yield the 4-bromo-5-oxo-azepane-1-carboxylic acid tert-butyl ester; ii) treatment of the 4-bromo-5-oxo-azepane-1-carboxylic acid tert-butyl ester with thioacetamide in ethanol in the presence of triethylamine at reflux to give the 2-methyl-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepine-6-carboxylic acid tert-butyl ester; iii) conversion of the 2-methyl-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepine-6-carboxylic acid tert-butyl ester into the 2-methyl-5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepine by removal of the tert-butyloxycarbonyl function with hydrogen chloride (aqueous, 37%) in methanol at room temperature.

c) 2-Methyl-6-(2-methyl-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-5-nitro-3H-pyrimidin-4-one

A suspension of 0.234 g (1.00 mmol) of the 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one, 0.205 g (1.00 mmol) of the 2-methyl-5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepine hydrochloride and 0.304 g (2.20 mmol) of potassium carbonate in 2.0 ml of N,N-dimethylformamide was stirred at room temperature for 60 hours. The reaction mixture was then poured into 50 ml of an ice/water mixture and the crystals formed collected by

filtration. Thus, a first crop of the 2-methyl-6-(2-methyl-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-5-nitro-3H-pyrimidin-4-one was obtained. The mother liquor was then evaporated and the residue chromatographed on silica gel using a 9:1 v/v mixture of dichloromethane and methanol as eluent giving a second crop of the 2-methyl-6-(2-methyl-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-5-nitro-3H-pyrimidin-4-one, in total 0.252 g (0.785 mmol, yield 78.5%) as light yellow solid; m.p. >200 °C; MS: $[M+H]^+$ = 322.

Example 2

6-(6-Ethoxy-2-methyl-5-nitro-pyrimidin-4-yl)-2-methyl-5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepine
and
3-Ethyl-2-methyl-6-(2-methyl-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-5-nitro-3H-pyrimidin-4-one

A suspension of 0.120 g (0.373 mmol) of 2-methyl-6-(2-methyl-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-5-nitro-3H-pyrimidin-4-one (example 1), of 0.070 g (0.45 mmol) of the ethyl iodide and of 0.077 g (0.56 mmol) of potassium carbonate in 1.0 ml of N,N-dimethylformamide was stirred at room temperature for 4 hours. The reaction mixture was then poured into 50 ml of an ice/water mixture and extracted 3 times with 50 ml of ethylacetate. The combined ethylacetate phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was then chromatographed on silica gel using a 95:5 v/v mixture of dichloromethane and methanol as eluent giving in a first fraction 0.025 g (0.072 mmol, yield 19%) of the 6-(6-ethoxy-2-methyl-5-nitro-pyrimidin-4-yl)-2-methyl-5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepine as yellow amorphous solid; MS: $[M+H]^+$ = 350.

The second fraction provided 0.081 g (0.23 mmol, yield 62%) of the 3-ethyl-2-methyl-6-(2-methyl-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-5-nitro-3H-pyrimidin-4-one as yellow solid after crystallization from ether; m.p. 164.2-166.8 °C; MS: $[M+H]^+$ = 350.

Example 3

6-(2-Amino-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-2-methyl-5-nitro-3H-pyrimidin-4-one

In analogy to the procedure described in example 1c 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one as prepared in example 1a was treated with 2-amino-5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepine [Ger. Offen. (1989), DE 3820775] in N,N-dimethylformamide in the presence of potassium carbonate at 110 °C to yield the title compound as yellow solid; m.p. >200 °C; MS: $[M+H]^+ = 323$.

Example 4

6-(2-Amino-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-3-ethyl-2-methyl-5-nitro-3H-pyrimidin-4-one

In analogy to the procedure described in example 2 the 6-(2-amino-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-2-methyl-5-nitro-3H-pyrimidin-4-one (example 3) was treated with the ethyl iodide in N,N-dimethylformamide in the presence of potassium carbonate at room temperature to yield the title compound as yellow solid; m.p. >200 °C; MS: $[M+H]^+ = 351$.

Example 5

7-(6-Hydroxy-2-methyl-5-nitro-pyrimidin-4-yl)-2-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepin-4-ol

In analogy to the procedure described in example 1c 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one (example 1a) was treated with the 2-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepin-4-ol (prepared from the corresponding N-benzyl derivative [Bull. Chem. Soc. Jap. (1971), 44(1), 153-8] by catalytic hydrogenation with palladium on charcoal) in N,N-dimethylformamide in the presence of triethylamine at room temperature to yield the title compound as yellow solid; m.p. >200 °C; MS: $[M+H]^+ = 333$.

Example 6

2-Methyl-5-nitro-6-(4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-3H-pyrimidin-4-one

a) 5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepine

The title compound was prepared by the following reaction sequence: i) treatment of 4-bromo-5-oxo-azepane-1-carboxylic acid tert-butyl ester (example 1 b) with phosphorous pentasulfide, formamide and triethylamine in dioxane at reflux to yield 4,5,7,8-tetrahydro-thiazolo[4,5-d]azepine-6-carboxylic acid tert-butyl ester; ii) conversion of 4,5,7,8-

tetrahydro-thiazolo[4,5-d]azepine-6-carboxylic acid tert-butyl ester into 5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepine by removal of the tert-butyloxycarbonyl function with hydrogen chloride (aqueous, 37%) in methanol at room temperature.

b) 2-Methyl-5-nitro-6-(4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-3H-pyrimidin-4-one

In analogy to the procedure described in example 1c 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one (example 1a) was treated with the 5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepine in N,N-dimethylformamide in the presence of potassium carbonate at room temperature to yield the 2-methyl-5-nitro-6-(4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-3H-pyrimidin-4-one as yellow amorphous solid; MS: $[M-H]^-$ = 306.

Example 7

2-Methyl-5-nitro-6-(5,6,8,9-tetrahydro-pyrimido[4,5-d]azepin-7-yl)-pyrimidin-4-ol

In analogy to the procedure described in example 1c 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one (example 1a) was treated with 6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine trihydrochloride [Bull. Chem. Soc. Jap. (1971), 44(1), 153-8] in N,N-dimethylformamide in the presence of N-ethyl-di-isopropylamine at room temperature to yield the title compound as yellow solid; m.p. >200 °C; MS: $[M-H]^-$ = 301.

Example 8

[rac]-6-(4-Hydroxy-4,5,7,8-tetrahydro-thieno[2,3-d]azepin-6-yl)-2-methyl-5-nitro-3H-pyrimidin-4-one

In analogy to the procedure described in example 1c 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one (example 1a) was treated with the [rac]-5,6,7,8-tetrahydro-4H-thieno[2,3-d]azepin-4-ol [J. Heterocycl. Chem. (1985), 22(4), 1011-16] in N,N-dimethylformamide in the presence of N-ethyl-di-isopropylamine at room temperature to yield the title compound as light yellow oil; MS: $[M-H]^-$ = 321.

Example 9

2-Methyl-5-nitro-6-(4,5,7,8-tetrahydro-thieno[2,3-d]azepin-6-yl)-3H-pyrimidin-4-one

According to the method described in example 1c 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one (example 1a) was treated with 5,6,7,8-tetrahydro-4H-thieno-[2,3-d]azepine [J. Heterocycl. Chem. (1985), 22(4), 1011-16] in N,N-dimethylformamide in the presence of N-ethyl-di-isopropylamine at room temperature to yield the title compound as yellow solid; m.p. >200 °C; MS: $[M-H]^-$ = 305.

Example 10

6-(6-Ethoxy-2-methyl-5-nitro-pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-thieno[2,3-d]azepine

and

3-Ethyl-2-methyl-5-nitro-6-(4,5,7,8-tetrahydro-thieno[2,3-d]azepin-6-yl)-3H-pyrimidin-4-one

In analogy to the procedure described in example 2 2-methyl-5-nitro-6-(4,5,7,8-tetrahydro-thieno[2,3-d]azepin-6-yl)-3H-pyrimidin-4-one (example 9) was treated with ethyl bromide in N,N-dimethylformamide in the presence of potassium carbonate at room temperature to yield 6-(6-ethoxy-2-methyl-5-nitro-pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-thieno[2,3-d]azepine as light yellow amorphous solid; MS: $[M+H]^+$ = 335; and 3-ethyl-2-methyl-5-nitro-6-(4,5,7,8-tetrahydro-thieno[2,3-d]azepin-6-yl)-3H-pyrimidin-4-one as yellow foam; MS: $[M+H]^+$ = 335.

Preparation of the labeled compound needed for the binding assay

1-Ethyl-2-methyl-6-oxo-4-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile

a) 1,1,2-Tritritio-2,3,4,5-tetrahydro-1H-benzo[d]azepine

The 1,1,2-tritritio-2,3,4,5-tetrahydro-1H-benzo[d]azepine was obtained by the following sequence:

i) reaction of the 1-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-ethanone [J. Heterocycl. Chem. (1971), 8(5), 779-83] with dibenzoylperoxide and N-bromosuccinimide in carbon tetrachloride at reflux yielded the 1-(5-bromo-1,2-dihydro-benzo[d]azepin-3-yl)-ethanone;

ii) hydrogenation of the 1-(5-bromo-1,2-dihydro-benzo[d]azepin-3-yl)-ethanone with tritium using Pd/C in methanol in the presence of triethylamine yielded the 1-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-ethanone;

iii) treatment of the 1-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-ethanone with conc. aq. hydrochloric acid in methanol gave the 1,1,2-tritritio-2,3,4,5-tetrahydro-1H-benzo[d]azepine.

b) *E*- and/or *Z*-2-cyano-3-methylsulfanyl-3-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-acrylic acid ethyl ester

A solution of 35 mg (0.16 mmol) of ethyl 2-cyano-3,3-bis(methylthio)acrylate, of 4.4 mg (0.024 mmol) of 1,1,2-tritritio-2,3,4,5-tetrahydro-1H-benzo[d]azepine hydrochloride, and of 10 mg (0.1 mmol) of triethylamine in 0.37 ml of ethanol was heated at reflux for 6.5 h. The reaction mixture was then evaporated and the residue chromatographed on 6 g Lichroprep silica gel Si-60 (25-40µm) using a 5:1 v/v mixture of toluene and ethyl acetate as eluent. Thus, 4.5 mg (0.014 mmol, yield 60%) of the *E*- and/or *Z*- 2-cyano-3-methylsulfanyl-3-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-acrylic acid ethyl ester was obtained.

c) 2-methyl-6-oxo-4-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile

A solution of 4.4 mg (0.014 mmol) of *Z*- and/or *E*-2-cyano-3-methylsulfanyl-3-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-acrylic acid ethyl ester, of 3 mg (0.032 mmol) of acetamidine hydrochloride and of 6.6 mg (0.044 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene in 1.0 ml of N,N-dimethylformamide was stirred at 100 °C for 2 hours. The reaction mixture was then partitioned between a 50:1 v/v mixture of dichloromethane and methanol and ice water acidified with about 2 ml 0.2 N hydrogen chloride. The organic phase was dried over anhydrous sodium sulfate. The crude product was chromatographed on 5 g Lichroprep silica gel Si-60 (25-40µm) using a 6:1 v/v mixture of toluene and methanol as eluent. There was thus obtained 2.2 mg (0.008 mmol, yield 57 %) of 2-methyl-6-oxo-4-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile.

d) 1-Ethyl-2-methyl-6-oxo-4-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile

A suspension of 2.2 mg (0.008 mmol) of 2-methyl-6-oxo-4-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile, of 16 mg (0.10 mmol) of ethyl iodide and of 4.3 mg (0.031 mmol) of potassium carbonate in 0.21 ml of N,N-dimethylformamide was stirred at room temperature for 3 h. The reaction mixture was then partitioned between ethyl acetate and ice water acidified with about 1 ml 0.2 N hydrochloric acid. The organic phase was dried over anhydrous sodium sulfate. The thus obtained crude product was purified by chromatography on 5 g Lichroprep silica gel Si-60 (15-25µm) using a 50:1 v/v mixture of dichloromethane and methanol as eluent to yield 1.8 mg (0.0058 mmol, yield 73 %) of the 1-ethyl-2-methyl-6-oxo-4-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile as colorless solid, MS: $[M(^3H_0)+H]^+ = 309$ (27%), MS: $[M(^3H_1)+H]^+ = 311$ (38%), MS: $[M(^3H_2)+H]^+ = 313$ (27%), MS: $[M(^3H_3)+H]^+ = 315$ (8%).

Example A

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	100
Powdered lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
Tablet weight	250

Example B

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	200
Powdered lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	400

Example C

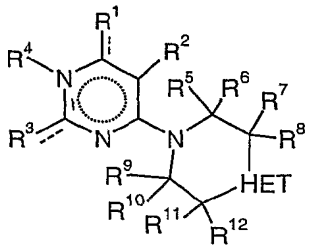
Capsules of the following composition are produced:

	mg/Capsule
Active ingredient	50
Crystalline lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	150

The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard gelatine capsules of suitable size.

Claims

1. Compounds of the general formula



wherein

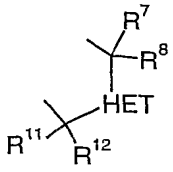
R^1 signifies oxygen, hydroxy, lower alkoxy or 2,2,2-trifluoroethoxy;

R^2 signifies nitro or cyano;

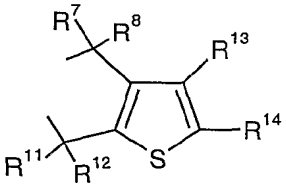
R^3 signifies hydrogen, lower alkyl, oxygen, lower alkoxy, amino, lower alkyl-amino or hydroxy-lower alkyl-amino;

R^4 signifies hydrogen, lower alkyl, lower alkenyl, or is absent, if the adjacent nitrogen atom already is the origin of three bonds as –N= or =N-;

R^5, R^6, R^9 and R^{10} signify, independently from each other, hydrogen or lower alkyl;

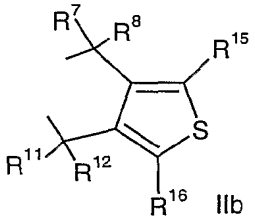


signifies

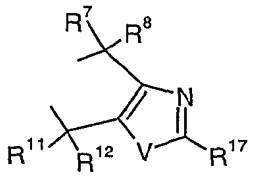


IIa

or



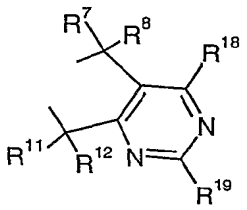
IIb



or

IIc

or



IId

R^7, R^8, R^{11} or R^{12}	signify, independently from each other, hydrogen, lower alkyl, or hydroxy;
R^{13} and R^{14}	signify, independently from each other, hydrogen or lower alkyl;
R^{15} and R^{16}	signify, independently from each other, hydrogen or lower alkyl;
R^{17}	signifies hydrogen, lower alkyl, lower alkoxy, hydroxy or amino;
R^{18}	signifies hydrogen or hydroxy;
R^{19}	signifies hydrogen, lower alkyl, lower alkoxy, hydroxy or amino;
V	signifies NH, S or O; and

the dotted line may be a bond,

as well as their pharmaceutically acceptable salts.

2. Compounds of formula I in accordance with claim 1, wherein R^2 is NO_2, and pharmaceutically acceptable salts thereof.

3. Compounds of formula I in accordance with claims 1 and 2, wherein R^1 is =O or lower alkoxy and HET represents a thiophene group, and pharmaceutically acceptable salts thereof.

4. Compounds of formula I in accordance with claim 3, which are

[rac]-6-(4-hydroxy-4,5,7,8-tetrahydro-thieno[2,3-d]azepin-6-yl)-2-methyl-5-nitro-3H-pyrimidin-4-one,

2-methyl-5-nitro-6-(4,5,7,8-tetrahydro-thieno[2,3-d]azepin-6-yl)-3H-pyrimidin-4-one,

6-(6-ethoxy-2-methyl-5-nitro-pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-thieno[2,3-d]azepine, or

3-ethyl-2-methyl-5-nitro-6-(4,5,7,8-tetrahydro-thieno[2,3-d]azepin-6-yl)-3H-pyrimidin-4-one.

5. Compounds of formula I in accordance with claims 1 and 2, wherein R^1 is =O or lower alkoxy and HET represents a thiazole group, and pharmaceutically acceptable salts thereof.

6. Compounds of formula I in accordance with claim 5, which are

2-methyl-6-(2-methyl-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-5-nitro-3H-pyrimidin-4-one,

6-(6-ethoxy-2-methyl-5-nitro-pyrimidin-4-yl)-2-methyl-5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepine,

3-ethyl-2-methyl-6-(2-methyl-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-5-nitro-3H-pyrimidin-4-one,

6-(2-amino-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-2-methyl-5-nitro-3H-pyrimidin-4-one,

6-(2-amino-4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-3-ethyl-2-methyl-5-nitro-3H-pyrimidin-4-one, or

2-methyl-5-nitro-6-(4,5,7,8-tetrahydro-thiazolo[4,5-d]azepin-6-yl)-3H-pyrimidin-4-one.

7. Compounds of formula I in accordance with claims 1 and 2, wherein R^1 is hydroxy and HET represents a pyrimidine group, and pharmaceutically acceptable salts thereof.

8. Compounds of formula I in accordance with claim 7, which are

7-(6-hydroxy-2-methyl-5-nitro-pyrimidin-4-yl)-2-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepin-4-ol, or

2-methyl-5-nitro-6-(5,6,8,9-tetrahydro-pyrimido[4,5-d]azepin-7-yl)-pyrimidin-4-ol.

9. A medicament comprising a compound of formula I according to any one of claims 1 to 8 as well as pharmaceutically acceptable salts thereof and pharmaceutically acceptable excipients.

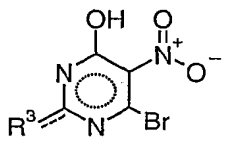
10. A medicament in accordance with claim 9 for the control or prevention of acute and/or chronic neurological disorders such as epilepsy, stroke, chronic and acute pain, psychosis, schizophrenia, Alzheimer's disease, cognitive disorders, memory deficits, restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest, hypoglycaemia, Huntington's chorea, ALS, dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression.

11. Compounds of formula I in accordance with any one of claims 1 to 8 as well as pharmaceutically acceptable salts thereof for use in the control or prevention of illness.

12. The use of compounds of formula I in accordance with any one of claims 1 to 8 as well as pharmaceutically acceptable salts thereof for the manufacture of a medicament for the control or prevention of acute and/or chronic neurological disorders such as epilepsy, stroke, chronic and acute pain, psychosis, schizophrenia, Alzheimer's disease, cognitive disorders, memory deficits, restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest, hypoglycaemia, Huntington's chorea, ALS, dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression.

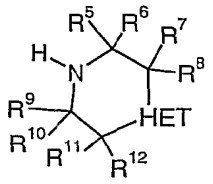
13. A process for the manufacture of compounds according to any one of claims 1 to 8 as well as of pharmaceutically acceptable salts thereof, which process comprises

a) reacting a compound of the formula



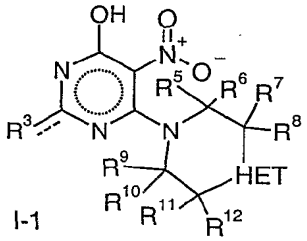
III

with a compound of formula



IV

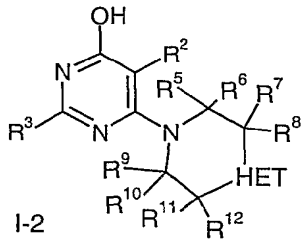
to a compound of formula



I-1

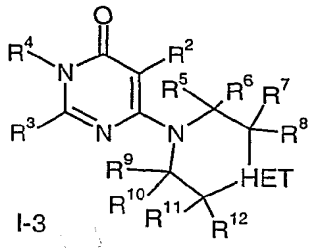
wherein R^3 and R^5 to R^{12} have the significance given above.

b) reacting a compound of formula



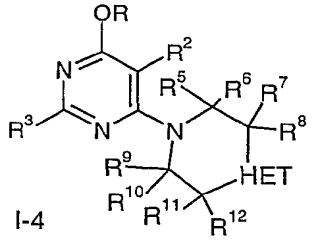
I-2

to a compound of formula



I-3

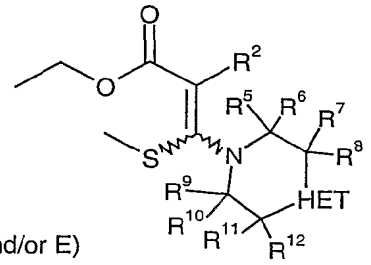
or to a compound of formula



I-4

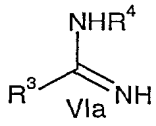
wherein R^2, R^3 and R^5 to R^{12} have the significance given above and R signifies hydroxy or lower alkyl, or

c) reacting a compound of formula



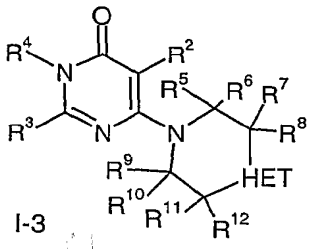
V (Z and/or E)

with a compound of formula



VIa

to a compound of formula



I-3

wherein the substituents have the significance given above,

and, if desired,

converting a functional group in a compound of formula I into another functional group and,

if desired,

converting a compound of formula I into a pharmaceutically acceptable salt.

14. Compounds of formula I in accordance with any one of claims 1 to 8, when manufactured by a process in accordance with claim 13.

15. The invention as herein described.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/EP 01/08186

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D495/04 C07D513/04 C07D487/04 A61K31/55 A61P25/00
//(C07D495/04,333:00,223:00),(C07D513/04,277:00,223:00),
(C07D487/04,239:00,223:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 804 849 A (GRISS G ET AL) 16 April 1974 (1974-04-16) column 16, line 47 -column 17, line 75; examples	1,9-12
A	DE 38 20 775 A (THOMAE GMBH DR K) 21 December 1989 (1989-12-21) cited in the application claims 1,7-10	1,9-12
A	US 3 940 395 A (SANTILLI ARTHUR A ET AL) 24 February 1976 (1976-02-24) column 3, line 22 - line 29; example XII	1,9-12
A	US 3 876 636 A (FAURAN CLAUDE P ET AL) 8 April 1975 (1975-04-08) column 7, line 18 -column 8, line 19; tables	1,9-12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
11 December 2001	02/01/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hass, C

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Inte nal Application No
PCT/EP 01/08186

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 105, no. 5, 4 August 1986 (1986-08-04) Columbus, Ohio, US; abstract no. 42679v, page 727; XP002185307 abstract & D FREHEL ET AL: J. HETEROCYCL. CHEM., vol. 22, no. 4, 1985, pages 1011-16,	1
A	CHEMICAL ABSTRACTS, vol. 74, no. 25, 21 June 1971 (1971-06-21) Columbus, Ohio, US; abstract no. 141677r, page 582; XP002185308 abstract & H YAMAMOTO ET AL: BULL. CHEM. SOC. JAP., vol. 44, no. 1, 1971, pages 153-8,	1
A	WO 92 07844 A (PFIZER) 14 May 1992 (1992-05-14) page 64, line 8 - line 10; claim 1; examples 126,127,133,134	1
A	EP 0 274 324 A (SANOFI SA) 13 July 1988 (1988-07-13) cited in the application	

INTERNATIONAL SEARCH REPORT

ormation on patent family members

Inte onal Application No
PCT/EP 01/08186

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3804849 A	16-04-1974	DE 2040510 A1	17-02-1972
		DE 2127267 A1	14-12-1972
		AT 310174 B	15-08-1973
		AT 310179 B	15-08-1973
		AT 310180 B	15-08-1973
		AT 310181 B	15-08-1973
		AT 310764 B	15-09-1973
		AT 310182 B	15-08-1973
		AU 462319 B	19-06-1975
		AU 3241171 A	22-02-1973
		BE 771330 A1	14-02-1972
		BG 17968 A3	05-03-1974
		BG 17785 A3	25-12-1973
		BG 17786 A3	25-12-1973
		CA 965423 A1	01-04-1975
		CH 561730 A5	15-05-1975
		CH 562829 A5	13-06-1975
		CH 571009 A5	31-12-1975
		CH 562830 A5	13-06-1975
		CH 571003 A5	31-12-1975
		CS 178084 B2	31-08-1977
		DK 136654 B	07-11-1977
		ES 393881 A1	16-09-1973
		ES 396451 A1	16-05-1974
		ES 396452 A1	16-05-1974
		ES 396453 A1	16-05-1974
		ES 396454 A1	16-05-1974
		FI 54925 B	29-12-1978
		FR 2102192 A5	07-04-1972
		GB 1321509 A	27-06-1973
		HU 162343 B	29-01-1973
		IE 35517 B1	03-03-1976
		IL 37492 A	14-03-1974
		JP 52046236 B	22-11-1977
		NL 7111176 A ,B,	16-02-1972
		NO 131887 B	12-05-1975
		RO 60635 A1	15-10-1976
		RO 59127 A1	15-02-1976
		RO 59322 A1	15-02-1976
		RO 59129 A1	15-01-1976
		RO 59925 A1	15-08-1976
		SE 380529 B	10-11-1975
		SU 442601 A3	05-09-1974
		SU 461507 A3	25-02-1975
		SU 503526 A3	15-02-1976
		SU 461508 A3	25-02-1975
		SU 474151 A3	14-06-1975
		US 3907996 A	23-09-1975
		YU 208471 A ,B	31-12-1979
		YU 288178 A ,B	31-12-1979
DE 3820775 A	21-12-1989	DE 3820775 A1	21-12-1989
		AT 106082 T	15-06-1994
		AU 617188 B2	21-11-1991
		AU 3659389 A	21-12-1989
		CA 1337195 A1	03-10-1995
		DD 284021 A5	31-10-1990
		DE 58907706 D1	30-06-1994

INTERNATIONAL SEARCH REPORT

ormation on patent family members

Inte ›nal Application No
PCT/EP 01/08186

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 3820775 A		DK 301689 A	21-12-1989
		EP 0347766 A2	27-12-1989
		ES 2057022 T3	16-10-1994
		FI 892991 A ,B,	21-12-1989
		HU 51630 A2	28-05-1990
		IE 64661 B1	23-08-1995
		IL 90650 A	13-05-1993
		JP 2045489 A	15-02-1990
		JP 2776892 B2	16-07-1998
		KR 130202 B1	09-04-1998
		NO 176357 B	12-12-1994
		NZ 229637 A	29-01-1991
		PT 90907 A ,B	29-12-1989
		SU 1731061 A3	30-04-1992
		US 5068325 A	26-11-1991
		ZA 8904636 A	27-02-1991
US 3940395 A	24-02-1976	NONE	
US 3876636 A	08-04-1975	FR 2158081 A1	15-06-1973
		AU 465951 B	09-10-1975
		AU 4811072 A	26-04-1974
		BE 790287 A1	19-04-1973
		CA 980775 A1	30-12-1975
		CH 551418 A	15-07-1974
		DE 2252822 A1	03-05-1973
		ES 407913 A1	16-11-1975
		FR 2225154 A2	08-11-1974
		GB 1339389 A	05-12-1973
		JP 927609 C	13-10-1978
		JP 49005979 A	19-01-1974
		JP 53005677 B	01-03-1978
		LU 66378 A1	03-05-1973
		NL 7214533 A	02-05-1973
		SE 398349 B	19-12-1977
		SU 490290 A3	30-10-1975
		ZA 7207579 A	25-07-1973
WO 9207844 A	14-05-1992	AT 124694 T	15-07-1995
		AU 644035 B2	02-12-1993
		AU 9059291 A	26-05-1992
		BR 9107070 A	31-05-1994
		CA 2095213 A1	07-05-1992
		CN 1061411 A	27-05-1992
		CZ 9204009 A3	15-12-1993
		DE 9190155 U1	07-10-1993
		DE 69111077 D1	10-08-1995
		DE 69111077 T2	02-11-1995
		DK 556310 T3	21-08-1995
		EP 0556310 A1	25-08-1993
		ES 2074867 T3	16-09-1995
		FI 932032 A	05-05-1993
		GR 3017122 T3	30-11-1995
		HU 64533 A2	28-01-1994
		IE 913854 A1	22-05-1992
		MX 9101913 A1	08-07-1992
		NO 931635 A	05-05-1993
		NZ 240476 A	27-04-1994

INTERNATIONAL SEARCH REPORT

formation on patent family members

Inte[illegible]nal Application No
PCT/EP 01/08186

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9207844 A		PT 99415 A	30-09-1992
		SK 400992 A3	09-08-1995
		US 5444062 A	22-08-1995
		WO 9207844 A1	14-05-1992
		ZA 9108767 A	05-05-1993
EP 0274324 A	13-07-1988	FR 2608607 A1	24-06-1988
		AT 60768 T	15-02-1991
		AU 602036 B2	27-09-1990
		AU 8252787 A	23-06-1988
		CA 1308729 A1	13-10-1992
		DE 3767993 D1	14-03-1991
		EP 0274324 A1	13-07-1988
		FI 875596 A ,B,	24-06-1988
		GR 3001816 T3	23-11-1992
		HU 48616 A2	28-06-1989
		IE 60381 B	13-07-1994
		JP 2113339 C	21-11-1996
		JP 8032702 B	29-03-1996
		JP 63166875 A	11-07-1988
		PT 86375 A ,B	01-01-1988
		US 4876362 A	24-10-1989